celerion

Applied Translational Medicine

Efficient Early Clinical Research to Achieve Clinical Proof-of-Concept Requires Patients

J. Fred Pritchard PhD

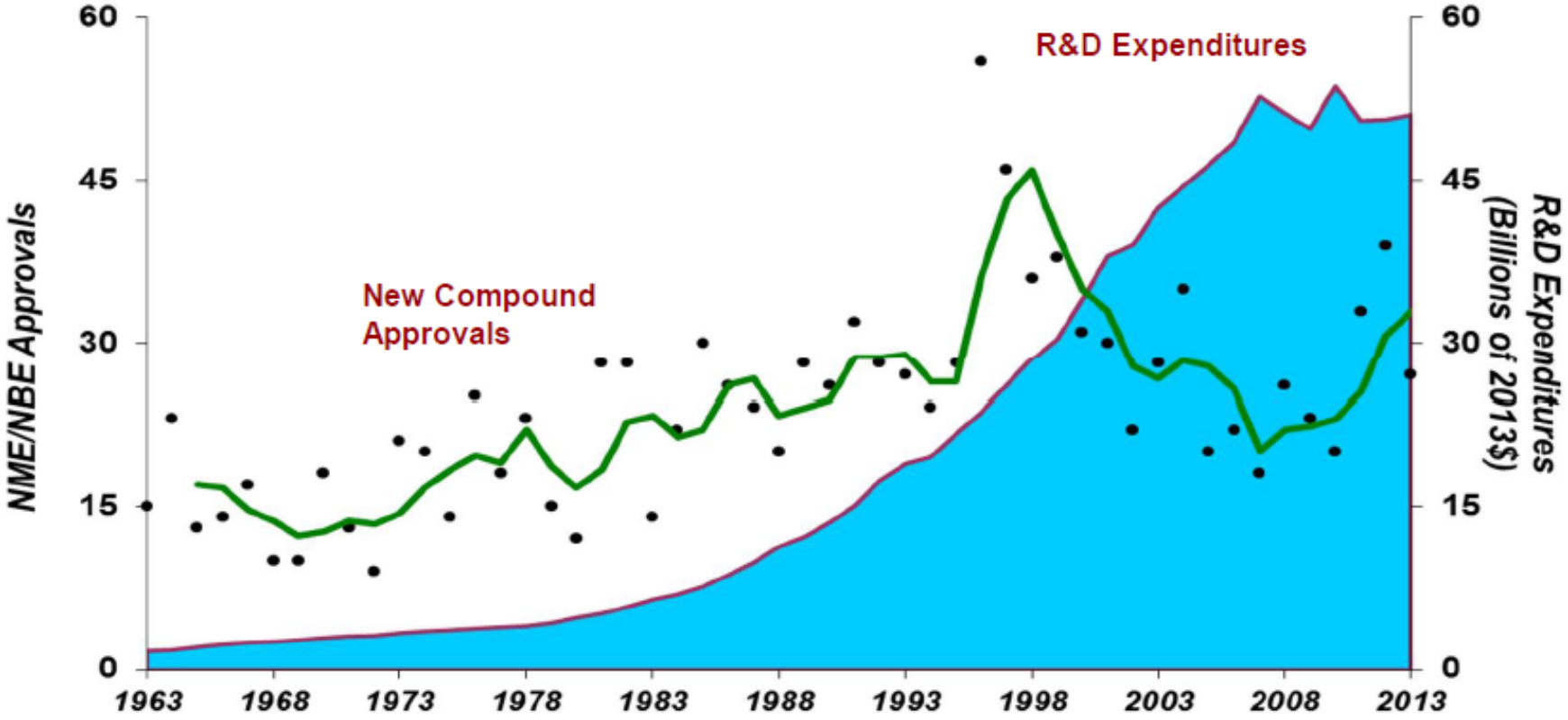
Vice President, Global Drug Development

Questions

- What are the latest measures of efficiency in drug development?
- How is early clinical research changing?
- What are some ways of making first-in-human studies more informative and efficient?
- What are some challenges and strategies for engaging patients in early clinical studies?
- What innovations are making early clinical research more efficient and effective?
- What are some challenges in conducting complex early clinical studies in patients?
- Is there globe warming to early clinical research?

celerion

New Drug And Biologics Approvals/R&D Spending

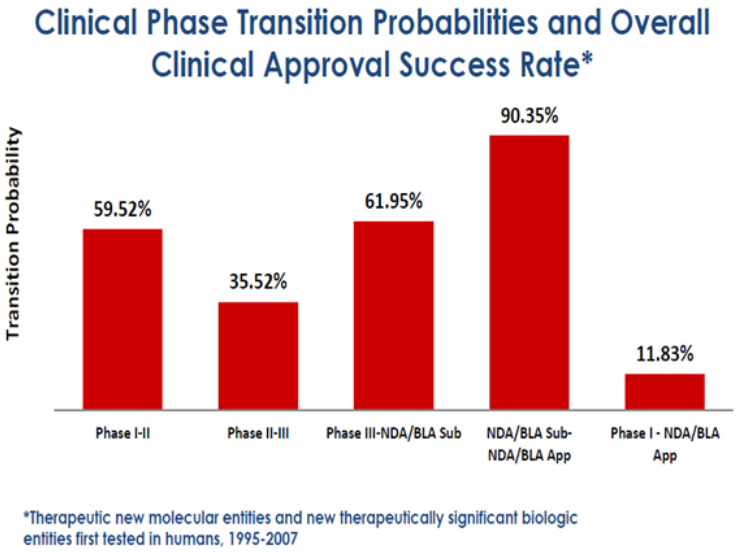


Reprinted with Permission: Tufts CSDD: PhRMA 2014 industry Profile

celerion

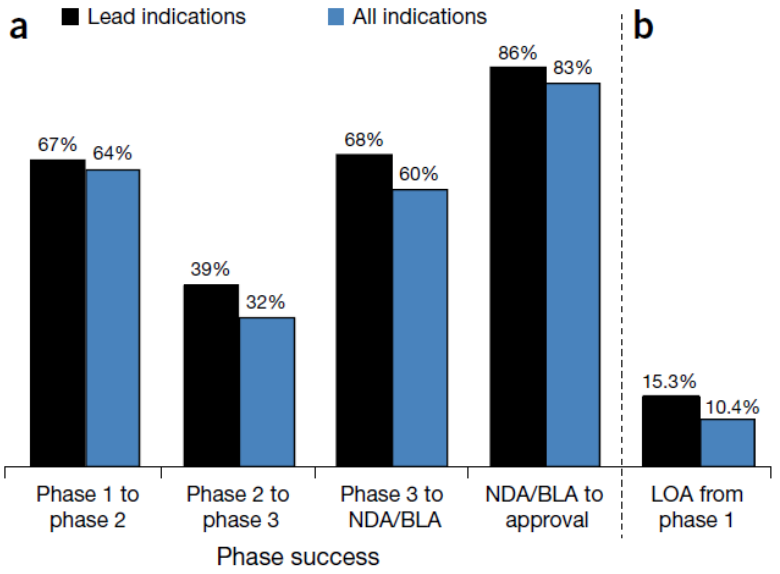
Phase Transition Rates

Tufts CDSS 2014



*Therapeutic new molecular entities and new therapeutically significant biologic entities first tested in humans, 1995-2007

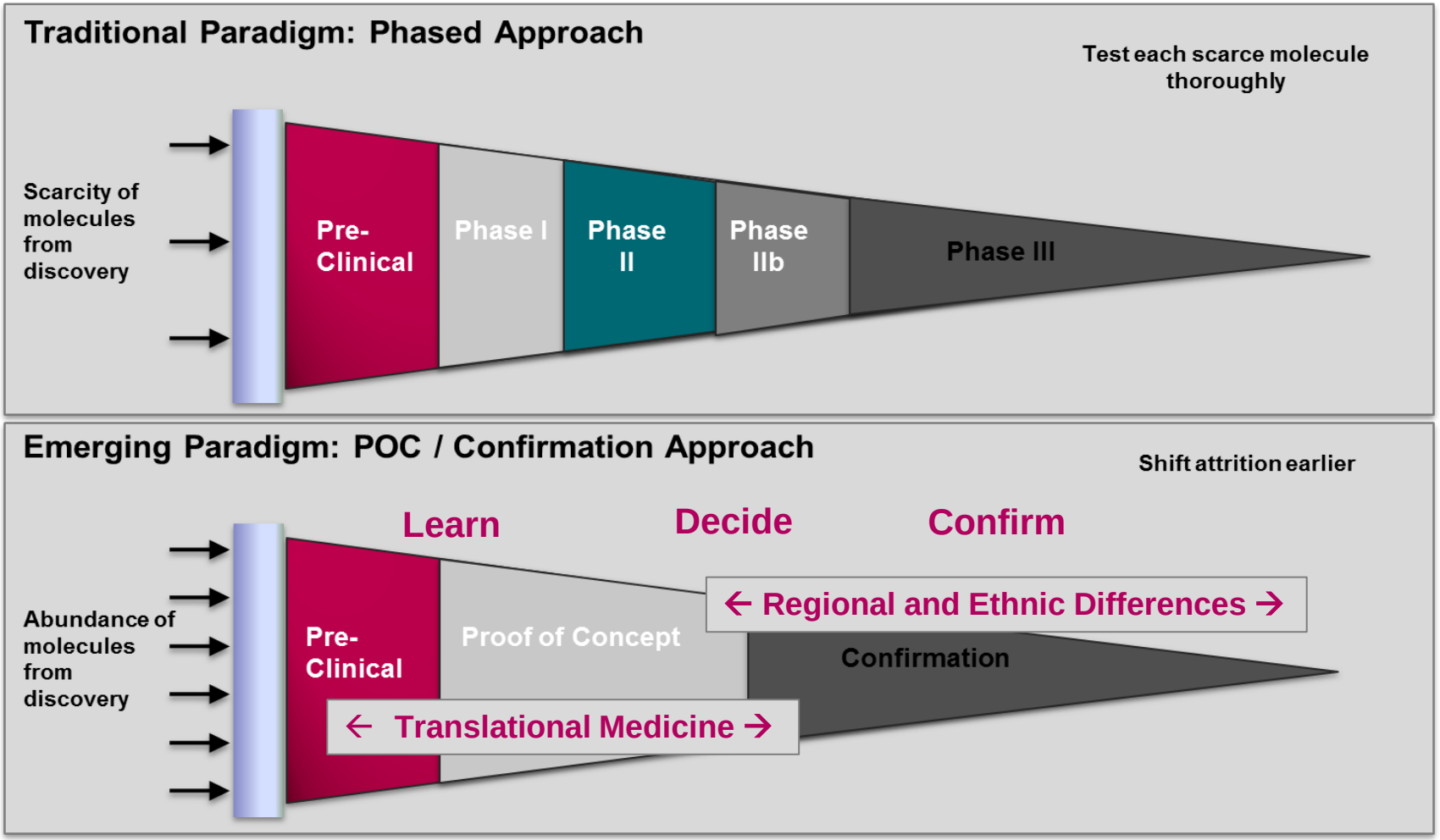
Hays 2014



Reprinted with Permission: Tufts CSDD: PhRMA 2014 industry Profile

celerion

Changing Paradigm



Source: William Blair & Company, (Bain and Company) Covance Investors Overview June 16, 2010

Searching for More Efficient Ways of Managing Risk in Drug Development

Engineered Process

- Stepwise
- Early studies structured same as later studies – primary objectives and endpoints
- Influenced by “rules-based” regulations

Preclinical

- Phase I: safety, tolerance, PK (healthy participants)
- Phase II: dose response (small groups of patients)
- Phase III: safety and efficacy (statistically robust)
- Phase IV: post-approval surveillance
- Global filings to each market
- Filings for new indications

Adaptive Development

- Feedback loops to discovery (Translational Medicine)
- Early studies fused with multiple objectives and endpoints
- Influenced by emerging “risk-based”guidances

Learn

- Preclinical
  - Human Microdose - PK
- Early Clinical: safety, tolerance, PK (healthy subjects and patients)
  - Proof-of-Presence
  - Proof-of-Mechanism
  - Proof-of-Concept
- Dose Response

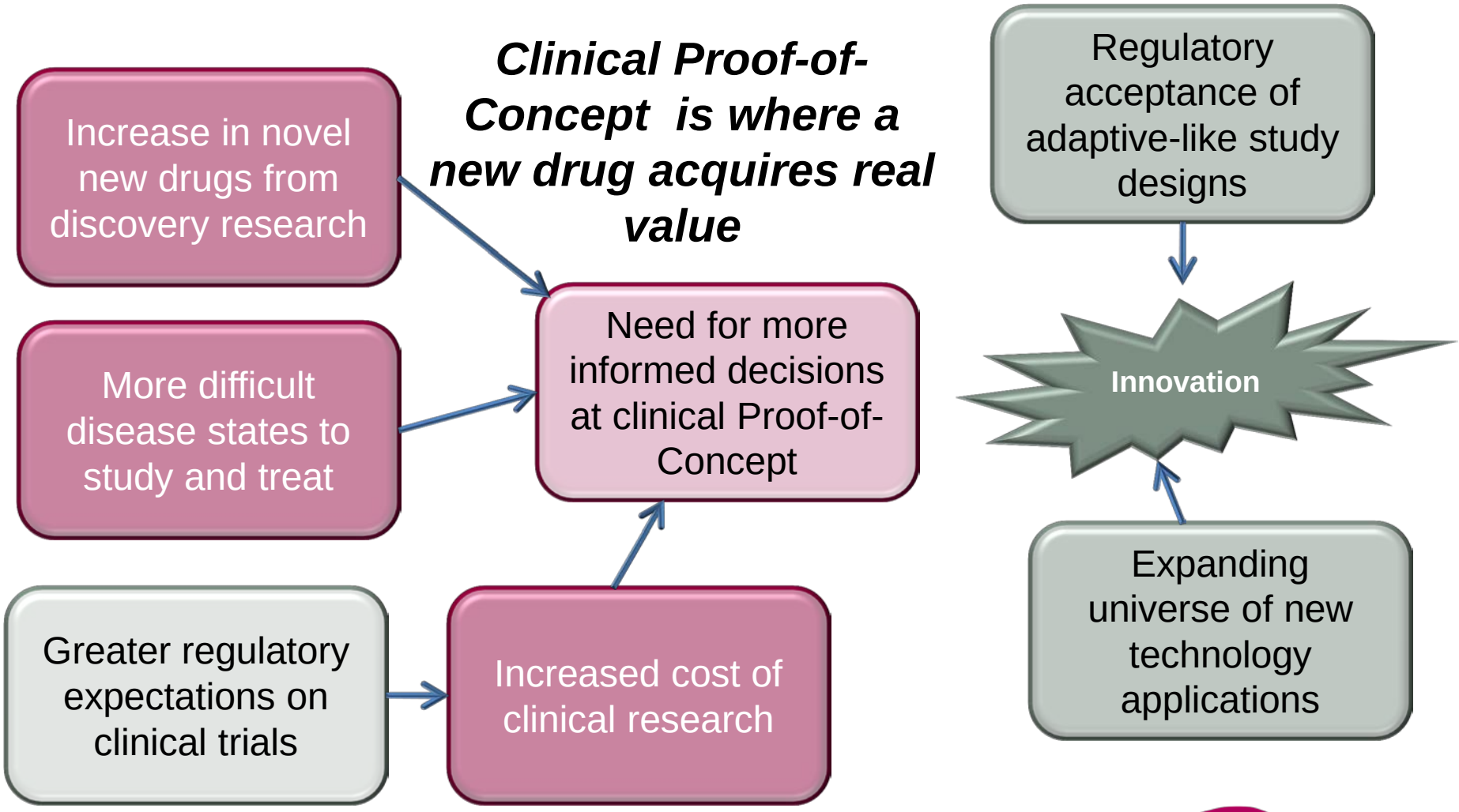
Confirm:

- Safety and efficacy (statistically robust)

Uptake:

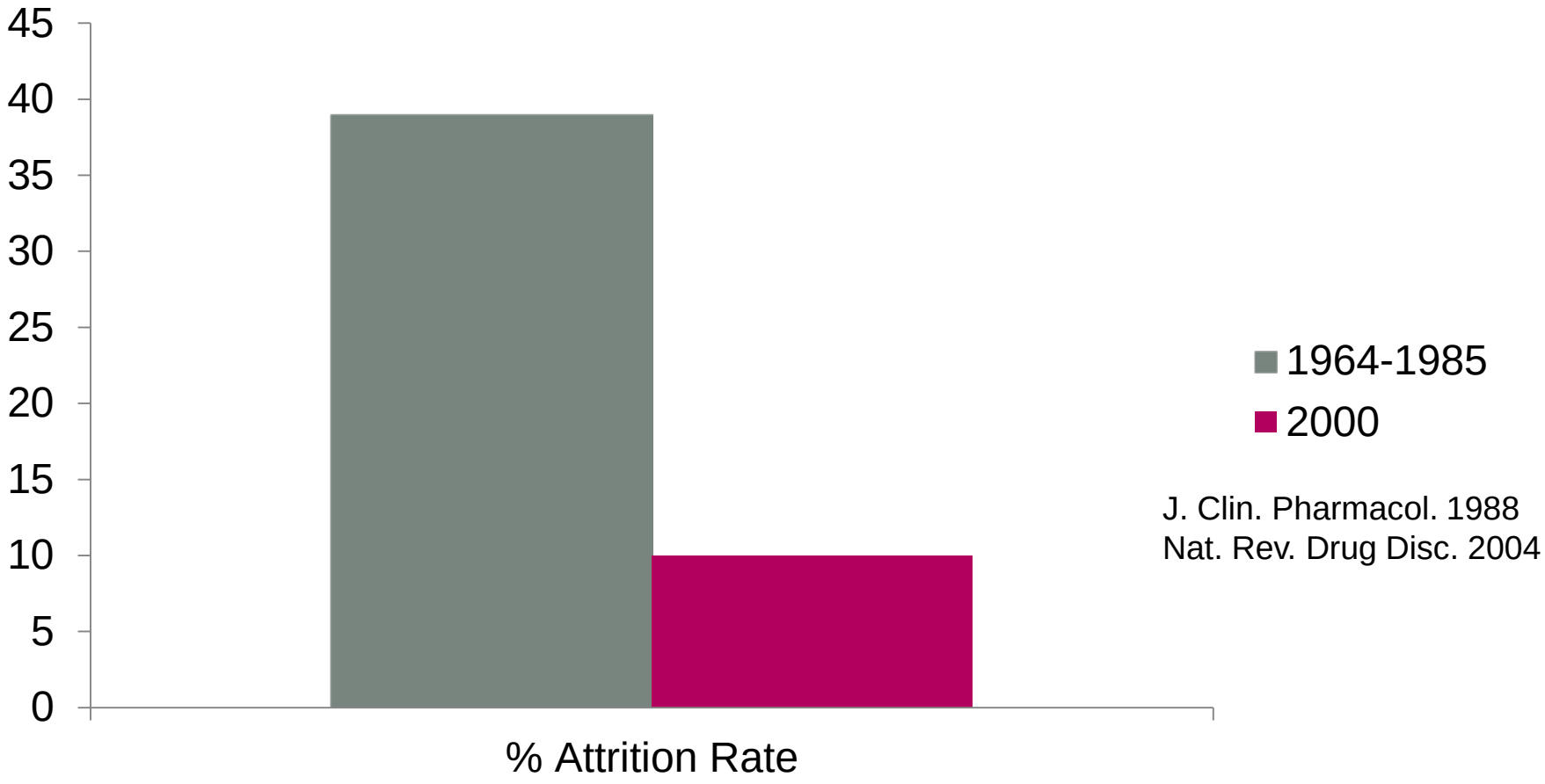
- Simultaneous global filings
- Post-approval surveillance
- Filings of new indications

What's Driving Evolution of New Paradigm?



celerion

Attrition Rate of NME Due to PK/ADME



J. Clin. Pharmacol. 1988
Nat. Rev. Drug Disc. 2004

NME: New Molecular Entity
PK: Pharmacokinetic
ADME: Absorption, Distribution, Metabolism & Excretion

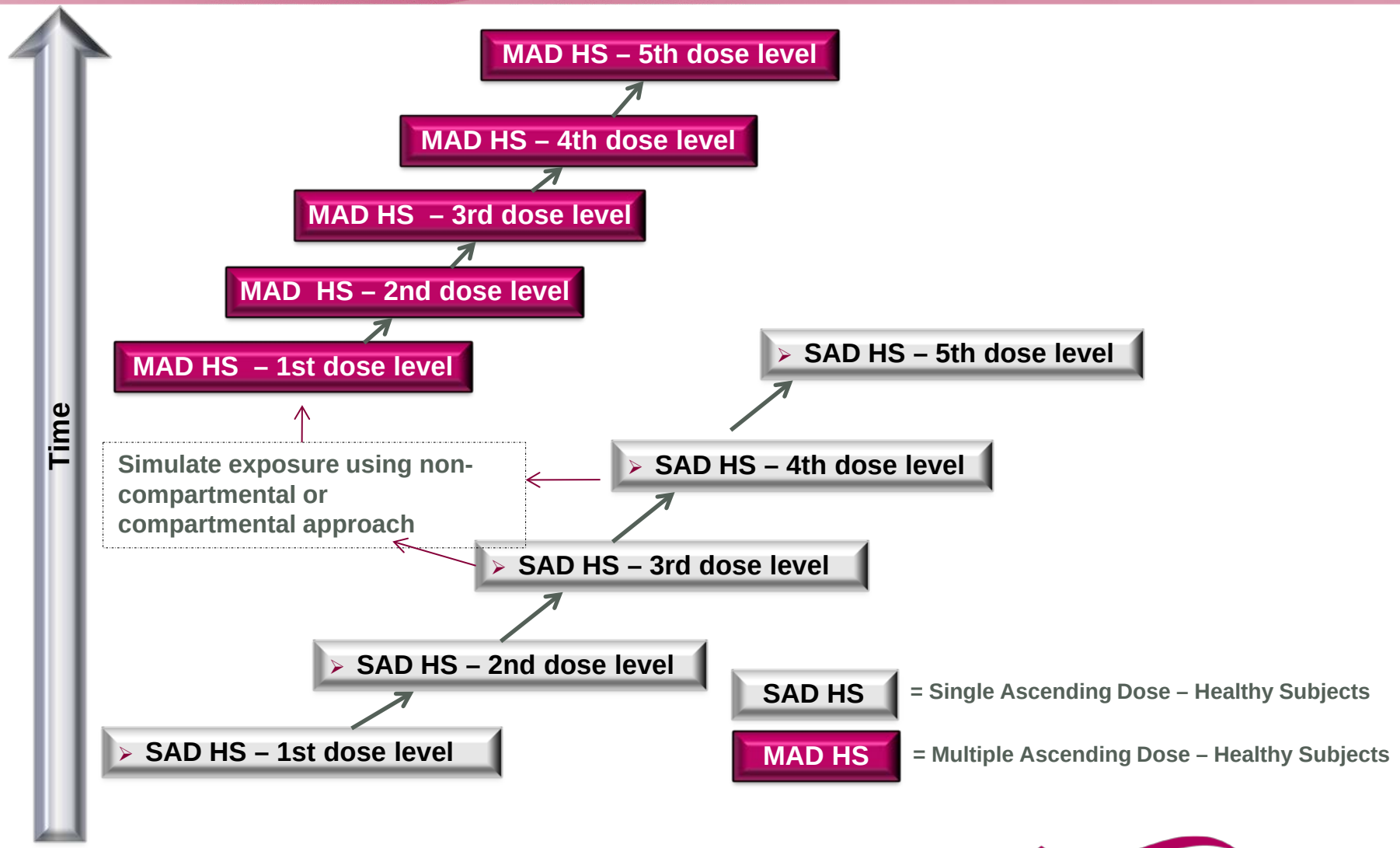
celerion

Characteristics of an Efficient First-in-Human Study

- Establishes drug does not elicit acute, treatment-limiting adverse events
- Characterizes the ADME properties:
  - Peak exposure
  - Overall exposure
  - Half-life
- Identifies influences for future patient exposure
  - Effect of food for oral dosing
  - Site of administration for Subcutaneous (SC)
  - Timing of dose
- Minimizes time and cost to Proof-of-Concept (POC) step

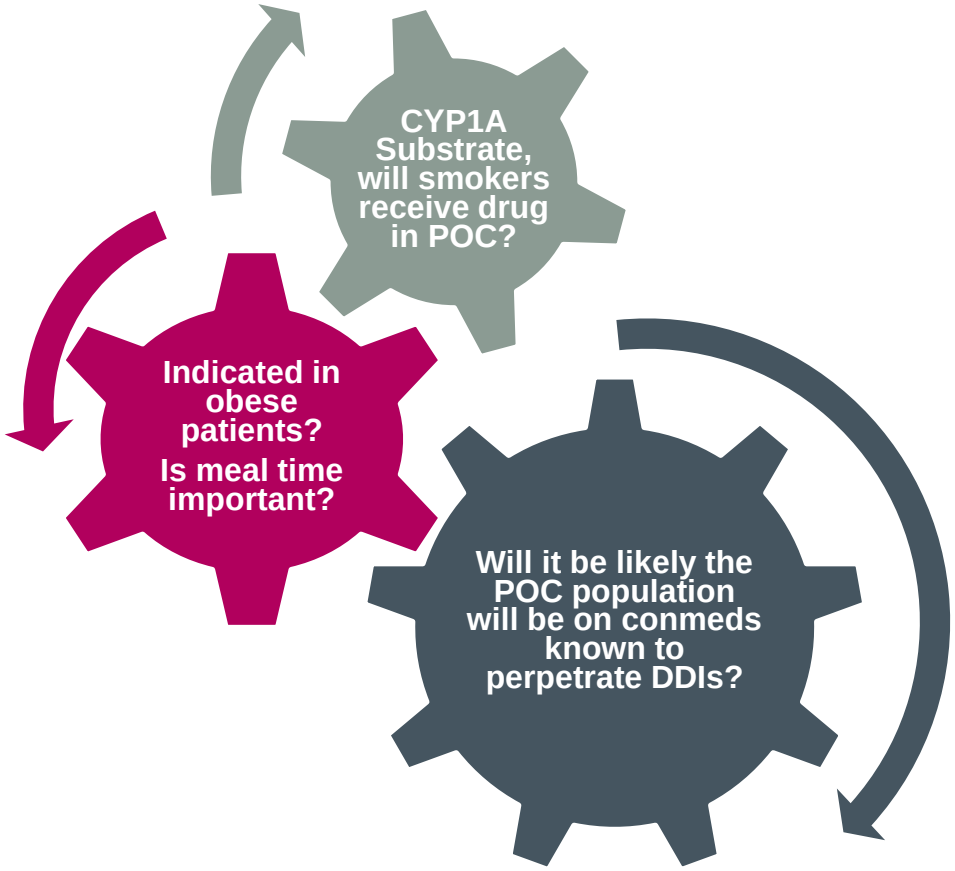
celerion

Efficient First-in-Human Designs



celerion

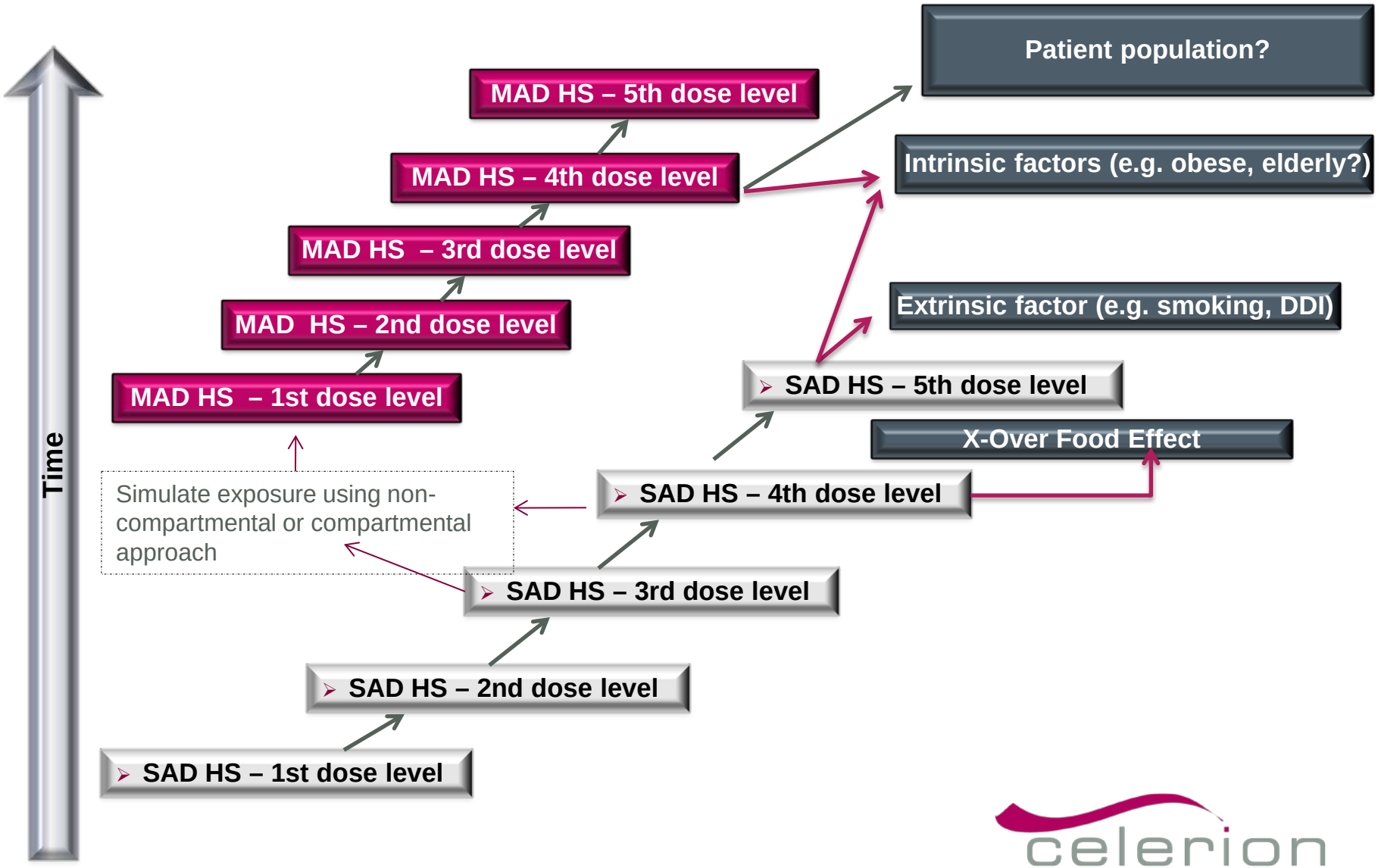
What Do We Know/Understand Regarding the Target Population?



CYP: Cytochrome P450 Enzyme
POC: Proof-of-Concept
DDI: Drug-Drug Interaction

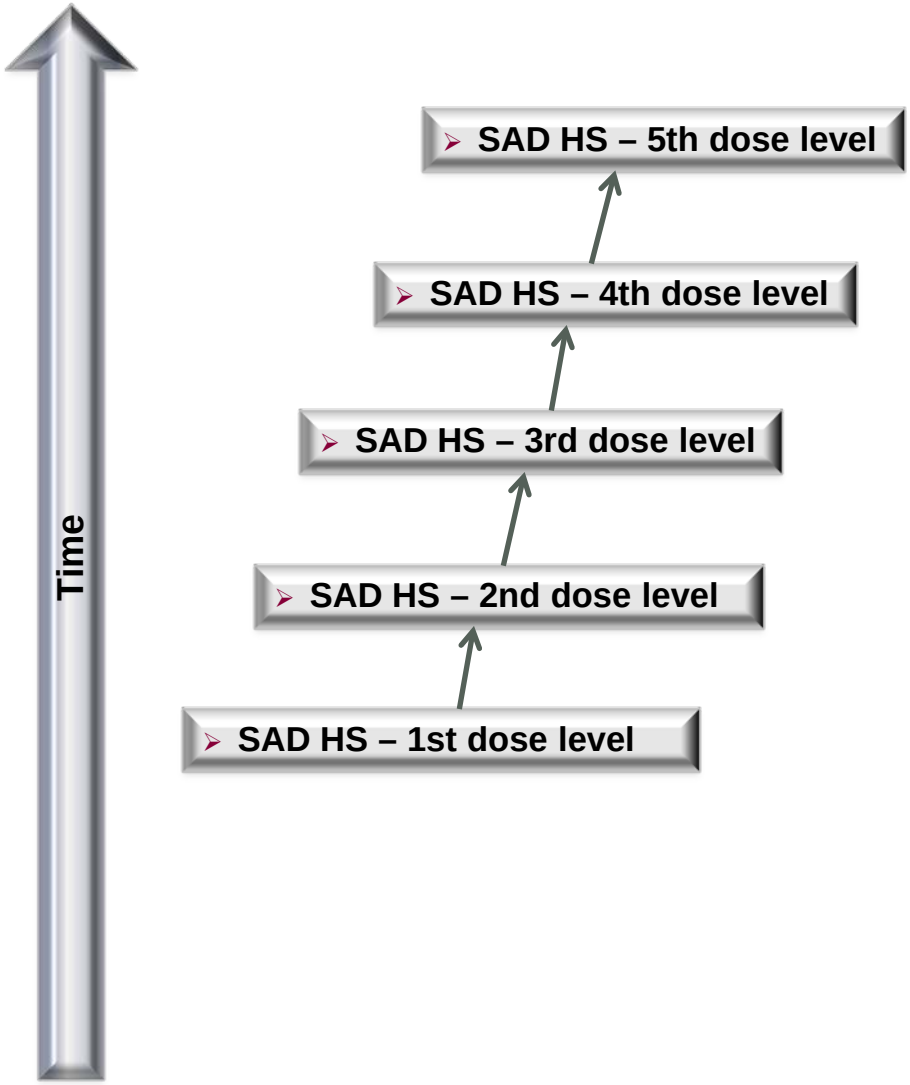
celerion

Integrate Intrinsic/Extrinsic Factors into SAD/MAD



celerion

Integrate Intensive Electrocardiographic (ECG) Monitoring for Early Cardiovascular Signal

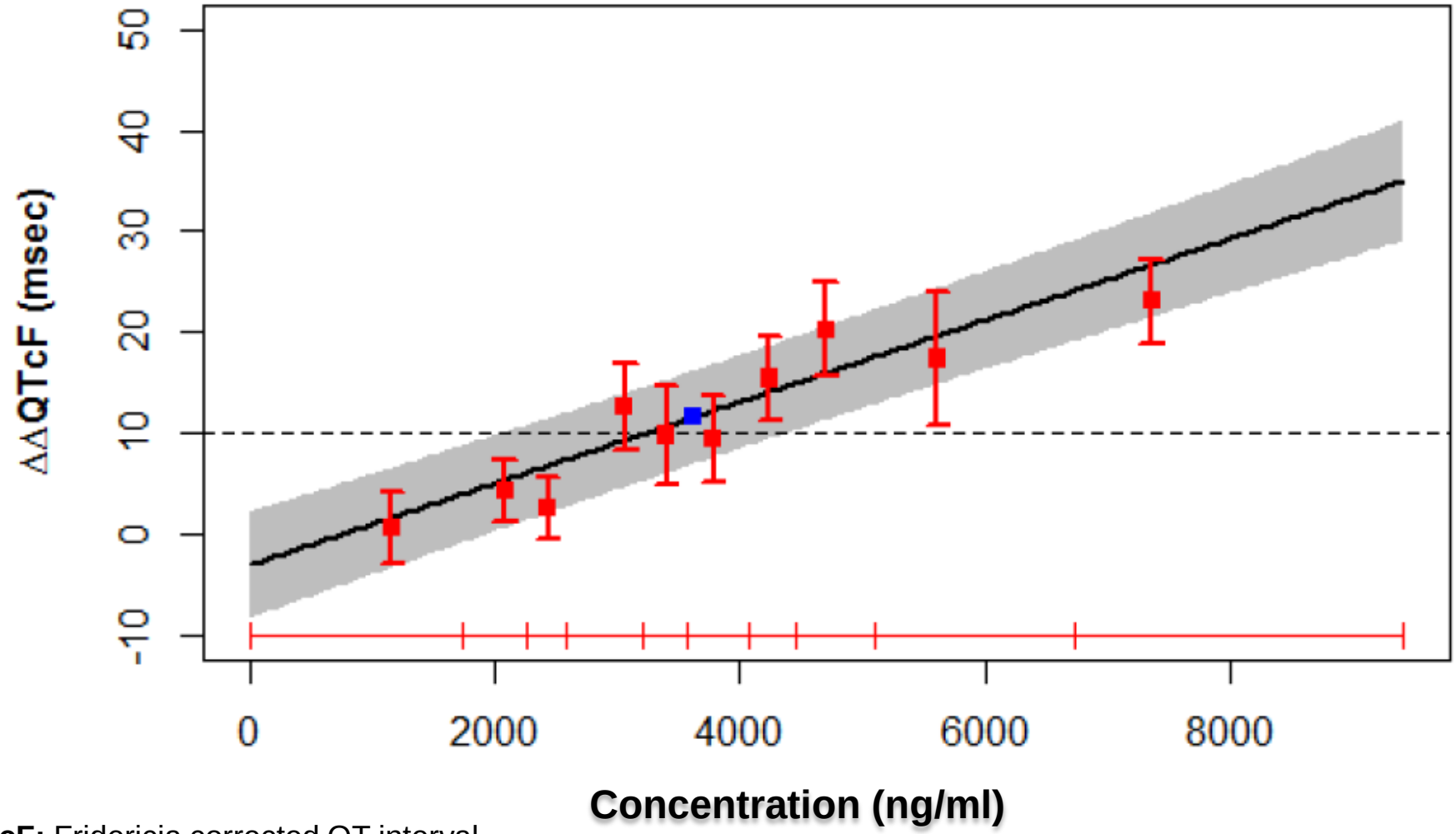


Each Cohort

- ECG Extractions
- Single 24hr Holter monitoring session
- Three triplicate baseline timepoints
- 6-9 triplicate post-dose timepoints
- Proactively plan for extended supine periods

celerion

SAD Allows for Evaluation of Potentially Supra-Therapeutic Exposure



QTcF: Fridericia corrected QT interval
msec: millisecond
Δ: Greek letter 'Delta' represents change from baseline, change from placebo

celerion

Important "Proofs" in Early Clinical Research

- **Proof-of-Presence**
  - Does the drug get to its site of action?
  - Value Add: $

- **Proof-of-Mechanism**
  - Does the drug affect the biological target as it was designed?
  - Value Add: $$$

- **Proof-of-Concept**
  - Is there a sufficient signal that the drug favorably impacts the disease with acceptable risk of toxicity that would stimulate further investment in the drug?
  - Value Add: $$$$$

- Pharmacokinetics
- Tissue concentrations
- Healthy subjects (HS) or patients

- Biomarkers reflecting target engagement
- Biomarkers of toxicity (liver, kidney effects)
- Healthy subjects or patients

- Biomarkers reflecting impact on disease
- Biomarkers of toxicity (liver, kidney effects)
- Patients

celerion

Early Signals of Clinical Safety and Efficacy are the Key to Applied Translational Medicine

To get an early sense that a drug is working in humans as it was designed, you need:

Patients

- Small number
- Stable disease
- Minimal confounding treatments
- Appropriately motivated

Investigators / Clinical Trial Units

- Small number of sites
- Scientifically / medically robust
- Controlled study setting
- Follow global GCP standards
- Ethical

celerion

Access to Patient/Special Populations and Specialists

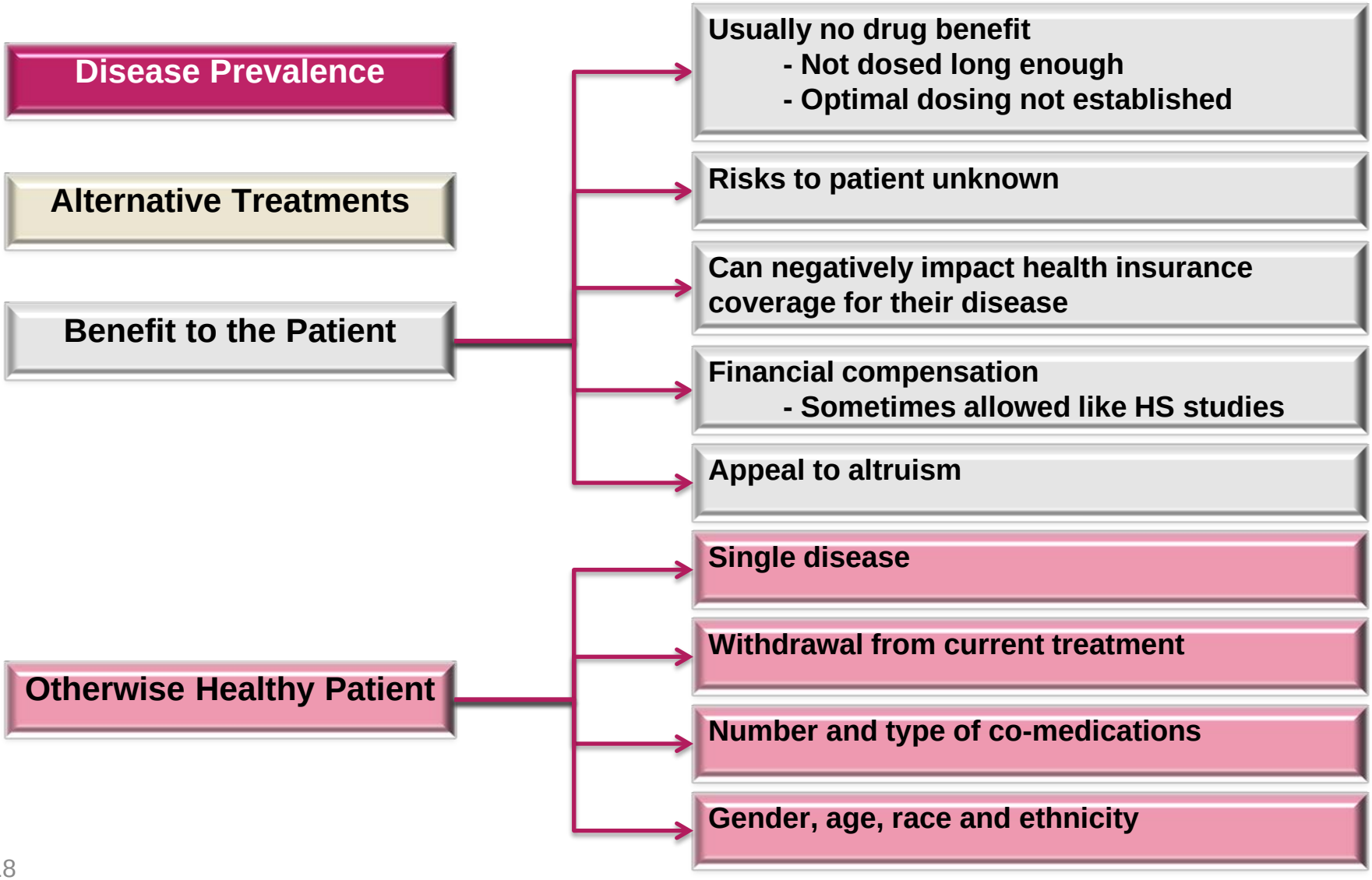
Special Populations

- Renal Impairment
- Hepatic Impairment
- Elderly
- Women
- Pediatric/Adolescent

Patient Populations

- Diabetes Mellitus
- Asthma
- Chronic Obstructive Pulmonary Disease (COPD)
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus (SLE)
- Psoriasis
- Alzheimer’s Disease
- Schizophrenia
- Depression
- Cancer
- Hypertension
- Hyperlipidaemia
- Infectious Diseases

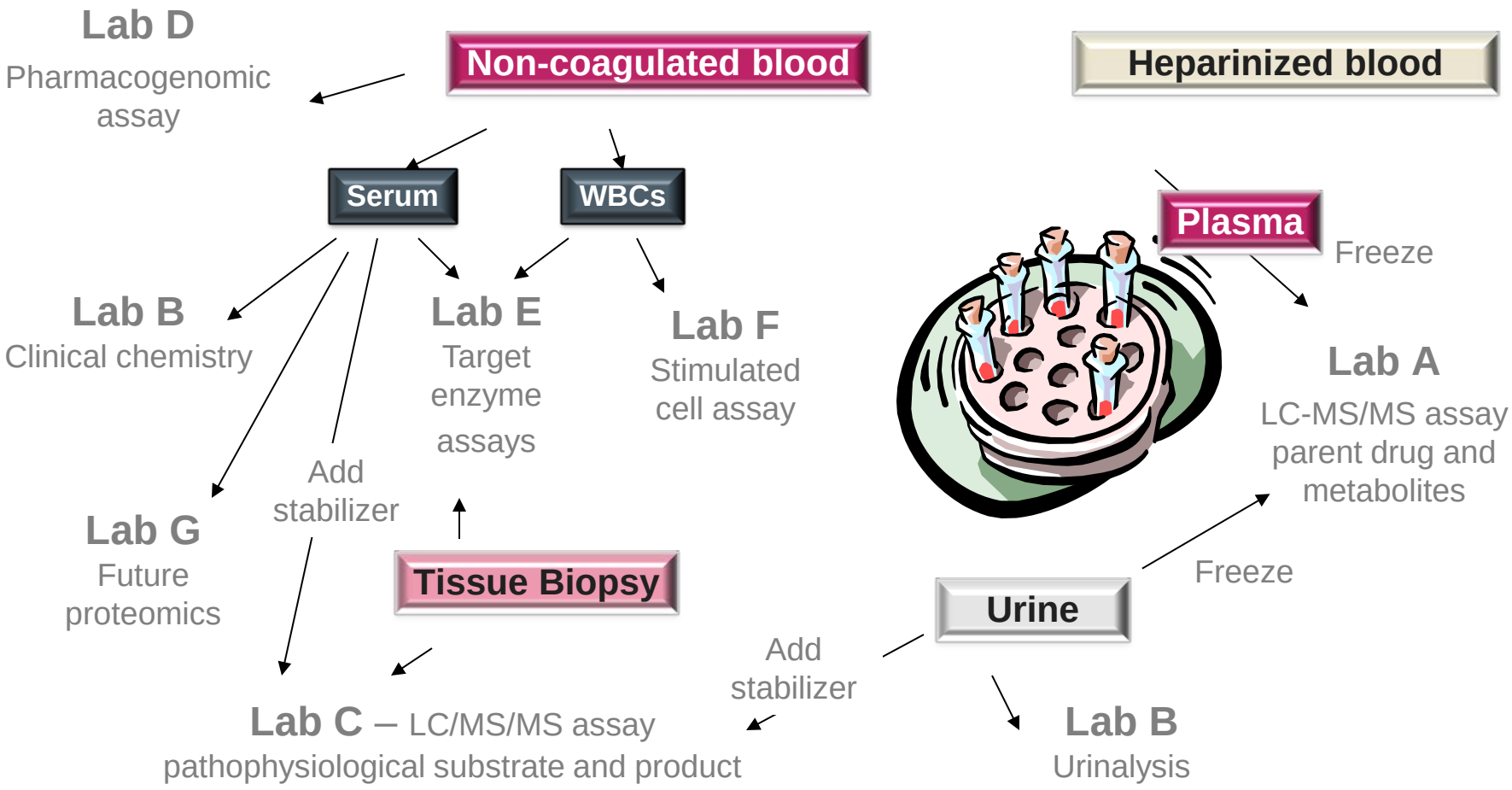
The Challenge of Recruiting Patients to Early Clinical Studies



Early Clinical Research Requires Resources Dedicated to Research

Complex sample collection schedules and processing procedures

Example: First-in-Patient study – 14 tests, 7 labs



A Perfect Scenario for Fast-to-Patient Strategy

- Single Ascending Dose (SAD) Study
- Novel Dipeptidyl Peptidase-4 (DPP4) Inhibitor in Mild Diabetic Patients
- No other drugs

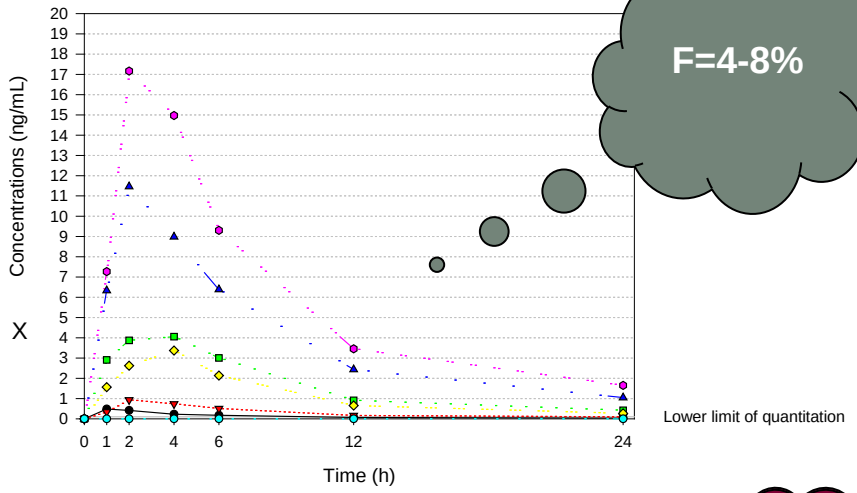
Sequence	Patients	Treatment Periods		
		P1	P2	P3
1 2 3	N = 5 N = 5 N = 5	PLA 25 mg 25 mg	75 mg PLA 75 mg	200 mg 200 mg PLA

Sequence	Patients	Treatment Periods		
		P'1	P'2	P'3
4 5 6	N = 5 N = 5 N = 5	PLA 50 mg 50 mg	100 mg PLA 100 mg	300 mg 300 mg PLA

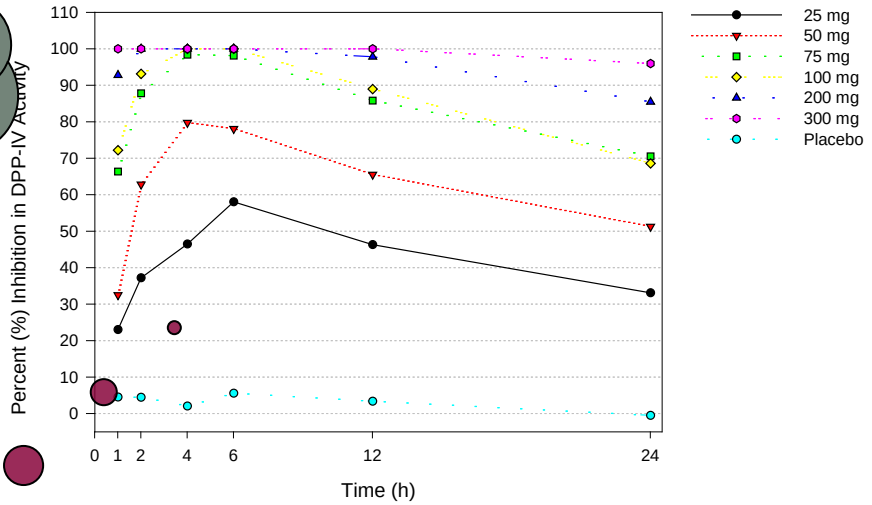
celerion

Results of SAD Study in Mild Diabetic Patients: *Early Evidence of Efficacy*

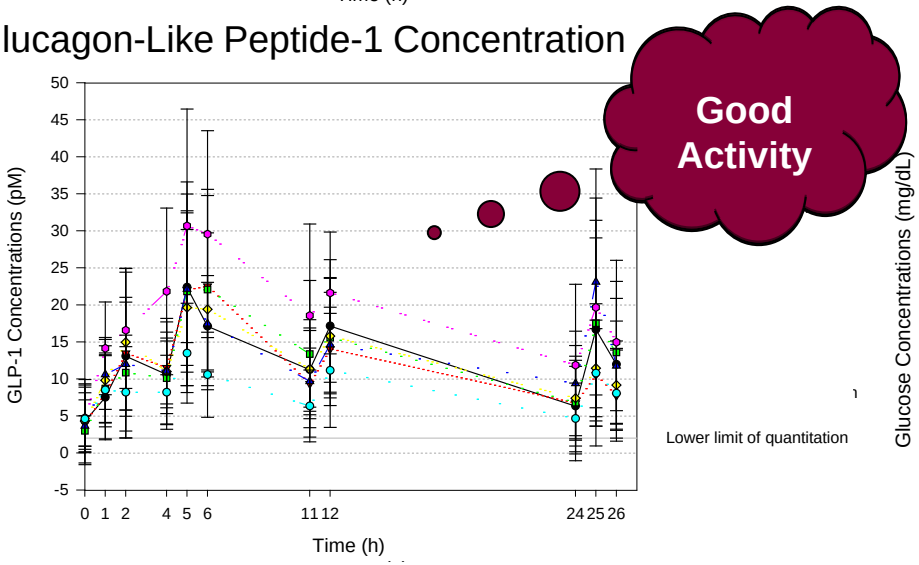
Drug Plasma Concentration



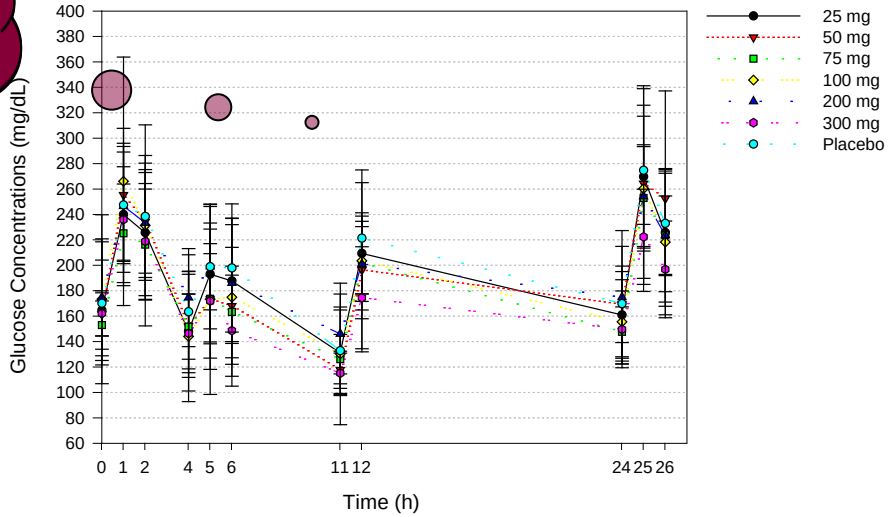
Percent DPP4 Inhibition



Glucagon-Like Peptide-1 Concentration



Glucose Concentration



Innovations in Early Clinical Research

- New Biomarkers of drug action and effect
  - Imaging (SPECT, functional MRI/PET), microRNAs, tracking genetic changes in tumors or microbiome, digital high resolution EEGs and ECGs
- Patient Recruitment
  - Social media tools to recruit patients
  - Electronic patient records to quickly assess impact of I/E criteria on recruitment and suitability of patients for a study
- Data Acquisition
  - Digital capture of data – real-time review and monitoring for quality
  - Video for remote viewing of study conduct in real time
  - Tablets and smart phones to capture patient data
  - Electronic tracking to confirm study compliance
- Data Analysis
  - Data repositories that allow comparison across studies and advanced modelling to predict drug response in specific patient settings

Global Clinical Pharmacology Unit Networks

- Most patient needs in early clinical research cannot be met by a single center
- Increasing the number of sites has its own challenges
- Need to evolve similar partnering and alliance models among groups of clinical pharmacology units
  - Work to same quality standards (undergo common systems Quality Assurance audits)
  - Coordinated through a group which also brings in other study services as protocol preparation, bioanalysis, pharmacokinetics, data management and statistics, clinical study report preparation

Celerion Locations and Partner Sites

A Global Network of Specialty Clinics and Labs

celerion

Examples of networks and therapeutic clusters

Patient Population	Celerion Site	External Site Network
Diabetes / Obesity	Phoenix Lincoln	Supporting networks in North America (NA), Europe, South Korea and Singapore
Respiratory and Inflammatory (asthma, COPD, cystic fibrosis)	Belfast	Strong network in UK and Germany (therapeutic cluster) Current US study at Temple Lung Center
Ophthalmology	Belfast Phoenix	Strong network in UK and Germany (therapeutic cluster)
Cardiovascular (hypertension, hypercholesterolemia, hyperlipidemia, thrombosis)	Belfast Phoenix	Strong networks in Europe and Korea (therapeutic cluster)
Oncology (blood, breast, colon, prostate, lung, pancreatic, ovarian, skin)		Strong networks in Korea (therapeutic cluster) Good access in Europe Major academic cancer centers dominate NA
Renal or Hepatic Insufficiency		Strong network in US and Europe
Rheumatoid Diseases (RA, OA, SLE)	Belfast	Strong networks in Korea and in Europe (therapeutic cluster)
CNS /Neurology (Alzheimer's, schizophrenia, anxiety, depression, pain, Parkinson's, convulsion)		Collaborative neuroscience network in US Good access in Europe and Korea
Infectious Disease (HIV, HCV, HSV, influenza, bacterial)		HCV – Europe and Korean sites (Asian phenotypes), Influenza/bacterial: access in Europe and Korea

Reasons for Performing Clinical Pharmacology Studies in Asia-Pacific Region

Market Drivers

1. Access to patients for early clinical assessment of safety, PK and signals of efficacy and dose response
2. Bridging PK and PK/PD studies to support registrations of drug products in Asian markets
3. Support First-in-Human assessments of drugs discovered and developed in Korea, Singapore, China, Japan and other Asian nations

Operational Factors

1. Modern, well equipped clinical trial centers at major medical centers with ready access to many patient populations
2. Some regulatory environments similar to North America and Europe
3. Well-trained scientific and medical staff that can communicate in English

Needs

1. Pharma companies need studies to support products for Asian markets
2. Asian clinical trial centers need access to global pharma study opportunities and best operating practices for running efficient operations

South Korea Has Developed the Resources Required to Support Early Clinical Research

Regulatory Environment in Five Asia/Pacific Countries

	Japan	China	South Korea	Singapore	Australia
Regulatory Review Time	No queries – 30 days after CTN submission	11 Months	30-60 Days	15-30 Days	No approval for healthy subject studies
Ethics / IRB Review Time	Variable	60 Days	2-4 Weeks	1-4 Weeks	12-16 Weeks (patients)
Parallel or Sequential	Parallel	Sequential	Parallel	Parallel	Clinical Trial Notification acknowledged in days
Clinical Trial Centers	Hospital and CRO-owned	SFDC-accredited CTCs	15 Hospital-based CTCs	1 Pharma-owned and 3 Hospital CTCs	5 Academic hospital clinics
Other Comments	Government funding new CTCs	Difficult to ship samples out of China	MFDS built on US FDA model	Translational medicine focus	Less CMC and preclinical safety

Audit Results of 7 Asian CTCs 2013-2014

Quality

- Most sites never had a full systems audit against global standards/ expectations
- Variability across sites in areas of strength and weakness
- Strengths: Across all sites were Phase I CTC facility and Security, Principal Investigator (PI) Oversight and Institutional Review Board (IRB) or Ethics Committee.
- Weaknesses: Staff Qualification records (6 of 7 sites), IT and Computer System Validation (4 of 7 sites), QA (4 of 7 sites), Vendor Management (4 of 7 sites), Staff Training Records (4 of 7 sites), Pharmacy (3 of 7 sites) and CAPA process (3 of 7 sites)

Five Key Elements of Clinical Success in Applying Translational Medicine

- **Expertise:** Scientific and medical staff with the portfolio of skills to design, conduct and interpret complex clinical studies
- **Experience:** Leveraging knowledge gained from conducting early clinical pharmacology studies with high density sampling
- **Facilities and Equipment:** Modern confinement clinics and laboratories equipped with innovative technologies to meet the varying and evolving demands of early clinical research
- **Access to Patients:** Recruiting the right participant or patient to meet the needs of specific study designs in a timely and ethical way.
- **Access to Biomarkers:** Leveraging capabilities resident within the participating clinics or laboratories or with qualified vendor labs to create the appropriate palate of tests to ascertain the drug's effect in humans

Bridging Strategy

Start design of CPoC study first

- What is “Proof”? Endpoints?
- What patients? How many?

How to get to CPoC?

- What can I do in healthy participants?
- Are biomarkers available?
- Develop novel biomarkers?
  - Biochemical assays
  - Imaging and imaging agents
  - MicroRNA panels
- Would microtracer studies be valuable?
- Can PK/PD modeling be applied?

What preclinical work is needed to support the early clinical program?

The Three Constraints

Brief Answers to Questions

- Latest metrics of efficiency in clinical research
  - ***10-15% of drugs entering clinical trials make it to market***
- How is early clinical research changing?
  - ***Focus on Clinical Proof-of-Concept – fail early***
- How are traditional FIH studies changing?
  - ***Fusion studies answering multiple questions on safety, PK, DDIs***
- What are some challenges and strategies for engaging patients early clinical studies?
  - ***Patient benefits vs risk***
  - ***Regional differences, patient networks***
- What are some challenges in conducting early clinical research studies in patients?
  - ***Access to biomarkers, specialty equipment and specialist researchers***
  - ***Sample logistics***
- What innovations are making early clinical research more efficient and effective?
  - ***Digital communications, real-time acquisition and access to data, apply complex analysis and modeling, new biomarkers***
- Why is there increasing attention to Asia-Pacific region in early clinical research?
  - ***Access to patients, modern clinical trial centers, educated staff, rapidly emerging biotechnology industry, large market***

celerion